

Improving quality of life for patients with chronic myeloid leukemia through supportive care, low-dose therapy, switching, and treatment-free remission

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Title: Improving quality of life for patients with chronic myeloid leukemia through supportive care, low-dose therapy, switching, and treatment-free remission

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Abstract:

Chronic myeloid leukemia (CML) is a hematologic malignancy that has become a largely manageable condition when treated with tyrosine kinase inhibitors (TKIs). However, the lifelong treatment course required for most patients is associated with side effects and toxicities that can impact patients' health-related quality of life (HRQOL). This review synthesizes current evidence on strategies to optimize HRQOL for patients on TKIs. This can be achieved through supportive care to manage TKI-related symptoms, dose adjustments, switching to a different TKI, or treatment discontinuation for select patients. We examine the clinical rationale and empirical support for each approach. Emphasis is placed on the importance of clear patient-physician communication and authentic shared decision-making and individualized care to address the needs and experiences of patients and to improve HRQOL.

Article Summary:

This review explores strategies to improve health-related quality of life (HRQOL) for patients with chronic myeloid leukemia (CML) receiving tyrosine kinase inhibitors (TKIs), focusing on supportive care, dose adjustments, switching therapies, and treatment-free remission.

Optimizing HRQOL in CML requires individualized, patient-centered management that includes symptom monitoring, shared decision-making, and active treatment adjustments rather than a one-size-fits-all approach.

Introduction

Treatment of chronic myeloid leukemia (CML) changed dramatically in 2001, when imatinib was introduced as the first molecularly targeted cancer therapy.¹ Imatinib, a tyrosine kinase inhibitor (TKI), induced disease response, markedly prolonged survival, and improved health-related quality of life (HRQOL) compared to the best available drug therapy at the time.² As an oral medication, imatinib was also more convenient for patients. Since the introduction of imatinib as the 1st generation (1G) TKI, other TKIs have since been developed and approved by the U.S. Food and Drug Administration to treat CML, including the 2nd generation (2G) TKIs dasatinib,³ nilotinib,⁴ and bosutinib,⁵ and 3rd generation (3G) TKIs ponatinib⁶ and most recently asciminib.^{7,8} The efficacy of TKIs mean that the prevalence of CML continues to rise, with nearly 75,000 cases in the US in 2022, according to SEER*Explorer.

While TKIs offer clear improvements over other treatment options, TKI use is associated with symptoms, with TKI users commonly reporting fatigue and gastrointestinal symptoms, fluid retention, and skin problems,⁹ especially when compared to peers without cancer.¹⁰ These symptoms in turn impair HRQOL, including physical, mental, and social well-being. Moreover, long-term TKI use is associated with toxicities thought to be caused by inhibition of kinases other than BCR::ABL1.¹¹ These toxicities include cardiovascular,^{12,13} renal,¹⁴⁻¹⁶ hormonal,¹⁷ neurological,¹⁸ and pulmonary¹⁹⁻²¹ adverse events. Finally, hematological adverse events, such as cytopenias, may persist or recur during treatment and impair HRQOL.²²

Despite the approval of generic imatinib in 2015, TKIs remain expensive, with per patient costs in the U.S. estimated at \$600 per year for generic imatinib to \$1,200,000 per year for 3G TKIs.^{23,24} Such high costs increase the financial burden on individual patients and their families and impact national health care expenditures. Moreover, it limits access to proper care; in one study of Medicare beneficiaries, nearly 1 in 3 older U.S. adults with CML had not initiated TKI treatment within 6 months of their diagnosis.²⁵ The cost and inconvenience of the molecular testing required to assess disease response is also an important consideration for patient

HRQOL. Across the U.S., Canada, Australia, the U.K., and Europe, monitoring typically follows a schedule of every 3 months until a major molecular response (MMR) is reached (BCR::ABL1 <0.1%), then every 3-6 months thereafter, unless a treatment change is made, when more frequent testing is required again.^{26,27} Requirements for frequent monitoring will affect some patients more than others, but the practical effects on patients' daily lives should not be discounted. Moreover, in some countries, the cost of molecular testing required to assess disease response is not insignificant; the direct effect of this on the patient varies by country and health insurance standards.

The vast majority of patients with CML can expect TKI treatment to control their disease. The management of the ~10% of patients who do not respond to TKI treatment is beyond the scope of this manuscript. About 30%-50% of patients on TKIs will achieve a sustained deep molecular remission (sDMR) and can attempt a treatment-free remission (TFR), and roughly half will be able to maintain that TFR long-term, effectively a cure for CML.²⁸ However, this means only 15%-25% of patients achieve TFR, while the other ~75%-85% of patients require life-long treatment, either because 1) they do not reach the sDMR needed to be eligible to try TFR, 2) because they have disease recurrence after attempting TFR, or in some cases, 3) because they are apprehensive about discontinuing their TKI and would prefer to maintain TKI therapy.²⁹

Patients receiving TKI therapy may reasonably be categorized into three groups based on their quality of life and treatment tolerance:

1. Well-Tolerated Group: Patients who experience minimal or no adverse effects from TKIs and maintain a good HRQOL.
2. Intolerant Group: Patients who develop significant side effects—such as persistent diarrhea or grade 3/4 laboratory abnormalities—that clearly necessitate dose reduction or switching to another TKI.

3. Intermediate Group: Patients who experience side effects that impact their HRQOL but are still able to continue TKI treatment. This group represents an area of clinical uncertainty where the decision to intervene is less clear.

To address this ambiguity, a panel was convened that included a patient, clinical experts (physicians, pharmacists, and an advanced practice registered nurse), and an expert in HRQOL measurement.³⁰ The panel used Delphi methodology to develop a consensus definition of TKI intolerance. The Delphi method is a formal, iterative process for consensus-building, which systematically combines opinions by asking panelists to provide information (often using a questionnaire), then discuss anonymized responses, and then provide the information again.³¹ For patients in the intermediate group, the Delphi panel's recommendation was for shared decision-making, recognizing that intolerance is often patient-specific. For example, a professional driver may find the common side effect of daily diarrhea unacceptable due to limited restroom access, whereas a computer programmer who works from home may not perceive it as a burden significant enough to require a change in treatment. Striking the right balance between avoiding premature TKI switching and preventing impairments in HRQOL is challenging, making open and ongoing communication between patients and clinicians essential.

For all patients on TKIs, treatment decisions should optimize HRQOL. HRQOL can be improved one of four ways: 1) supportive care to manage symptoms and prevent toxicities, 2) using a lower dose of the TKI to reduce toxicity, 3) switching to a different TKI, or 4) TFR (for eligible patients). Each strategy is examined in terms of its clinical application and impact on HRQOL.

Supportive care to manage symptoms and prevent toxicities

Many symptoms attributed to TKIs may be expected to improve with time,²⁷ so helping patients manage any symptoms should be the first method to try to improve patient HRQOL. We found one published empirical evaluation of supportive care for TKI-associated fatigue: a randomized controlled trial of cognitive behavioral therapy (CBT) vs. usual care in 44 patients with CML, which showed a significantly and clinically meaningful improvement in fatigue with CBT.³² However, while such direct evidence for supportive care management in CML is limited, there are numerous guideline- and expert-based approaches for managing common symptoms (Table 1) that draw on evidence from symptom management in other malignancies.²⁷ These options include behavioral modifications (e.g., sleep hygiene for sleep disturbances) and medical management (e.g., ondansetron for nausea). For some symptoms, identifying contributing factors (e.g., anemia exacerbating fatigue) or underlying conditions (e.g., dyspnea due to edema vs. pleural effusions) will help guide management. Given time pressures in clinic visits, there is an important role for midlevel practitioners in supportive care.³³

In addition to symptom management, supportive care strategies aimed at prevention of toxicities may also be appropriate. Chiefly, given the known cardiovascular risks of TKI use³⁴, prevention of cardiovascular toxicities should be encouraged through blood pressure and lipid control as well as healthy diet and exercise. While there are no empirical studies evaluating whether lifestyle changes can prevent TKI-related toxicities, there is strong evidence for these approaches to reduce atherosclerotic cardiovascular disease in general. For patients initiating on nilotinib or ponatinib, evaluation by a cardio-oncologist is warranted.

Management of more serious adverse events and toxicities requires more than supportive care or prevention. Hematologic, cardiovascular, pulmonary, renal, and neurologic toxicities should be treated using dose interruptions, dose reductions, and switching to a different TKI; these are addressed in the subsequent sections.

Dose Reduction

If supportive measures do not lead to symptom improvement or if the patient has a more serious toxicity, and the patient has an adequate disease response based on guidelines, then the next consideration should be reducing the dose of TKIs.³⁵ This section describes what is known about the efficacy of dose reductions and associated effects on HRQOL. From clinical experience, many patients report an improvement in symptoms with dose reductions. However, very few studies have empirically evaluated long-term TKI dose de-escalation,³⁶ and none have published final results that include patient-reported outcomes (PROs). Thus the evidence for the effects of dose on HRQOL is limited to clinician-reported adverse events. Table 2 summarizes the key studies on dose reductions.

Imatinib, bosutinib, dasatinib, nilotinib, and asciminib are the FDA-approved frontline therapies for patients with newly diagnosed CML. Their approvals were based on trials comparing “standard dose” TKI to previous treatments.^{3-5,37} In these trials, dose reductions were indicated for significant adverse events; no reductions were indicated based on disease response. The safety of a lower dose TKI has been demonstrated in several small studies, either starting with a lower dose or reducing the dose when patients respond.

In a phase II study from MD Anderson Cancer Center, dasatinib was given at 50 mg daily instead of the FDA approved dose of 100 mg. Of the 81 patients enrolled, 81% achieved a major molecular response (MMR) at 12 months. This was significantly higher than the randomized phase III trial of dasatinib vs. imatinib in which MMR rates were 46% for dasatinib and 28% for imatinib. The rates of adverse events, specifically pleural effusions, was lower compared to historical controls.³⁸

A lower starting dose of once daily nilotinib has not been evaluated as frontline therapy. This is despite the original phase I trial demonstrating that a dose of 400 mg daily was associated with response and a trough level of 1000ng/ml.³⁹ That level was well above the therapeutically effective dose. A strategy of “induction” with nilotinib at full dose given twice daily

followed by a once daily “maintenance” when patients are in MMR was shown to be safe and feasible in the NILO-RED study.⁴⁰ Although not commonly used, therapeutic drug monitoring may have benefit for patients on TKI therapy. Some,^{41,42} but not all studies⁴³⁻⁴⁵ found a correlation between trough levels and response to imatinib. Based on the original IRIS trial of imatinib, fluid retention, muscle cramps, rash, myalgia, and anemia were more common in patients in the 4th quartile with imatinib level >1170 ng/ml. Responses correlated with steady state trough levels on day 29. A level of approximately 1000 ng/ml seems to have the best response to toxicity benefit ratio. Dasatinib dose reduction based on trough levels was also shown to be feasible. Most patients could reduce to 50mg daily and still maintain disease response.^{46,47}

One of the largest studies was the DESTINY trial.⁴⁸ The goal in the DESTINY trial was treatment discontinuation, which was attempted in patients with a BCR::ABL1 < 0.1% (MMR) who maintained that response following one year of dose reduction. Overall, 80% of patients maintained BCR::ABL1 < 0.1% with dose reduction. Of those patients who then attempted discontinuation, 50% were successful in maintaining a TFR. It is not known what would have happened if those patients had stayed on a lower dose TKI and not attempted TFR. A separate retrospective study also demonstrated that a lower dose TKI does not compromise the chances for a successful TFR.⁴⁹

One of the few studies that prospectively evaluated the safety and efficacy of dose reduction the OPTIC trial of ponatinib.⁵⁰ Ponatinib is a very effective drug, but it was found to be associated with a significant increased risk of cardiovascular toxicity.⁵¹ This reported increased risk of cardiovascular toxicity led to early termination of the frontline study of imatinib vs. ponatinib in the EPIC study.⁵² With this early termination, the efficacy of ponatinib in the frontline setting could not be assessed. Based on the increased cardiovascular toxicity, the OPTIC trial was designed to allow for ponatinib dose reduction once patients achieved an adequate response, defined as BCR::ABL1 <1%. The OPTIC trial enrolled patients with resistant CML

with or without the T315I mutation. Patients were randomized to one of three arms: ponatinib 45 mg, 30 mg, or 15 mg. For the 45 and 30 mg arms, the dose was reduced to 15 mg once BCR::ABL1 <1%. The study demonstrated that the best benefit/risk ratio was starting with 45 mg and reducing to 15 mg, once patients achieved a response, especially for patients with a T315I mutation. Bosutinib is known to cause significant diarrhea at initiation that gradually resolves. This significant diarrhea at initiation leads to frequent treatment discontinuation in the first few weeks. To avoid that, the BOGI trial (BOsutinib Gradual Increase) evaluated starting with a lower dose of bosutinib (200 mg) and slowly escalating by 100 mg every 2 weeks in the absence of grade 2 or higher AEs. In the BOGI trial, the discontinuation rate dropped to 11%, compared to the historical rate of 32%.⁵³ In the phase I/II studies of bosutinib in patients with resistant CML, approximately 30% of patients received reduced bosutinib dose to 300 or 400 mg. Despite the dose reduction, efficacy was maintained, and the response rate was similar to patients who did not reduce the dose.⁵⁴

The ongoing Danish RODEO study is the first prospective study to use patient education and shared decision making to make TKI dose reduction decisions. Eligibility included BCR::ABL1 < 0.1%, though 91% of the 147 patients enrolled had a deeper response of < 0.01%. A strict threshold for disease response is used, if even one PCR shows BCR::ABL1 > 0.1%, TKI doses are increased again. With 12 months of follow up on 97 patients, 13% have increased their dose again.^{55,56} RODEO included PROs, both the EORTC QLQ-C30 and QLQ-CML24 were administered. The interim results show medium-sized improvements in social functioning and small improvements in fatigue, GI symptoms, impact on daily life, and body image.

A distinct but related strategy to reduce side effects and improve HRQOL is to use intermittent dosing. In the INTERIM study (intermittent imatinib),⁵⁷ patients older than 65 years old who had at least a cytogenetic response on imatinib started intermittent doses of imatinib, one month on and one month off. Half of patients maintained their disease response, and no

patient progressed to a more advanced phase. The study did not include measurement of HRQOL. For the 20 of 76 patients who reported side effects, half of them said these went away on the intermittent dosing schedule (particularly muscle pain, cramps, and fluid retention).

Switching to a different TKI

If a patient experiences intolerance despite symptom management and dose reduction, then a discussion of switching to a different TKI is warranted. Some patients are hesitant to switch despite having side effects that are significantly affecting their HRQOL, feeling that switching means they are weak or have failed if they cannot handle the side effects. It is important to discuss with patients that they may feel better on a different TKI, and that switching is common. Across clinical studies, approximately 20-40% of patients ultimately switch from their initial TKI.^{3,58-60}

The choice of TKI will depend on the reason for intolerance, patient comorbidities, and line of therapy. Some general concepts are:

- Avoid switching to another TKI that is commonly associated with the same side effect, e.g., if a patient is experiencing diarrhea, avoid switching to imatinib or bosutinib.
- Avoid rapid switching for patients who are on later lines of therapy.
- Select the next TKI based on patient comorbidities, e.g., avoid dasatinib in patients with pulmonary problems, avoid imatinib and bosutinib in patients with gastrointestinal symptoms, avoid nilotinib and asciminib in patients with history of pancreatitis, and avoid nilotinib and ponatinib in patients with history of cardiovascular problems. Patient age also plays a factor in the decision, as patients are more likely to have more comorbidities with advancing age.

Cross-intolerance occurs when the same side effect persists even after switching to a different TKI. This has been observed among 2G TKIs following a switch from imatinib.

Hematologic toxicities tend to persist post-switch, whereas non-hematologic adverse effects often improve. Bosutinib as 2nd or 3rd line after imatinib was overall well tolerated with 62% of patients experiencing the same AE, but only 16% discontinuing due to same AE.

Thrombocytopenia and pancytopenia were the most common reasons for discontinuation for same AE. Of the 13 patients who discontinued imatinib for diarrhea, 11(84.6%) experienced diarrhea of any grade, 5 (38.5%) experienced grade 3/4 diarrhea and 7.7% discontinued bosutinib due to diarrhea. Similarly, the rates of thrombocytopenia and discontinuation for thrombocytopenia with bosutinib after dasatinib were high, with 100% of patients experiencing thrombocytopenia and 38.5% discontinuing for thrombocytopenia. Patients who develop a pleural effusion with dasatinib have a high chance of developing pleural effusions with bosutinib and therefore that should be avoided if possible.^{61,62} Overall there is minimal non hematological cross intolerance for dasatinib after imatinib therapy.^{63,64} Hematological toxicity leading to discontinuation of dasatinib occurred in 13% of patients. Nilotinib after imatinib was also well tolerated with minimal cross intolerance for non-hematological toxicity. Only 6% of patients developed cross intolerance to the non-hematologic side effects and none of the patients discontinued for the same AE they had developed while on imatinib.⁶⁵ Hematological toxicity remained significant with over half of the patients developing hematological toxicity, mainly thrombocytopenia, and all 7 patients who discontinued therapy did so for recurrent thrombocytopenia. The ASC2ESCALATE trial⁶⁶ evaluated asciminib as 2nd line therapy after progression or intolerance to one prior TKI. Most patients who transitioned to asciminib due to intolerance to prior TKIs largely remained on therapy, suggesting a low incidence of cross-intolerance.⁶⁷ However, detailed data about cross intolerance from this cohort have not yet been published.

Attempting a treatment-free remission

For patients who are in a sustained deep molecular response, an attempt at TKI discontinuation and a TFR is warranted. To reach a sustained deep molecular response, TKI adherence is critical. Previous systematic reviews of interventions to improve adherence to TKIs have found that the most effective interventions have included multiple components (education, reminders, and structured follow-up) and have involved pharmacist and nurses⁶⁸⁻⁷⁰.

There have been multiple trials of TFR⁷¹. Two large studies of TFR have published on patient-reported HRQOL, which we now discuss in detail.

The U.S. Life After Stopping TKIs (LAST) study was the first to demonstrate that TKI discontinuation results in clinically meaningful improvements in a broad range of PROs, assessed using NIH PROMIS PRO measures, in particular, reduced fatigue and diarrhea⁷² and improved social functioning.⁷³ While about 1/3 of participants experienced an increase in pain in the first 3 months after TKI discontinuation (termed TKI withdrawal syndrome), the LAST study also showed that such increases in pain were transitory, returning to normal by 6 months.⁷⁴ The LAST study was also used to estimate costs for US adults using a TKI, attempting discontinuation with increased molecular monitoring, and reinitiating TKI therapy, if clinically appropriate. It was shown that attempting discontinuation of TKI therapy could save the U.S. healthcare system over \$54 billion during the next 30 years.⁷⁵

The EURO-SKI⁷⁶ trial was a large TKI discontinuation study conducted in 11 European countries. Using EORTC QLQ-C30 and FACIT-Fatigue PRO measures, it showed improvements in diarrhea and nausea/vomiting among the 686 participants who completed PRO measures. Younger patients (18-59) reported sustained improvements in fatigue, as well as role and social function. The youngest age group (18-39) reported improvements in cognitive function. Finally, increased pain was observed in 23% of participants and was associated with longer time on TKI treatment and older age.

Long-term studies are ongoing to evaluate the long-term effects of TFR, but it is likely that TFR may eliminate many of the more serious toxicities associated with extended TKI use, for example, dasatinib-associated pleural disease.⁷⁷ Yet, continued monitoring is needed, both to confirm sustained CML control as well as to screen for late-effects of prolonged use of TKIs remains, such as organ injury and vascular occlusive disease (nilotinib and ponatinib).^{78,79}

For patients who would like to discontinue but have not achieved the required deep molecular response, studies are ongoing to help them reach deep responses.^{80,81} Likewise, for patients who were not successful in their 1st TFR attempt, ongoing studies are testing new approaches to a 2nd TFR attempt.^{82,83}

Conclusion

To improve HRQOL for patients with CML, active management is needed. An approach of “pick a TKI, set it and forget it,” does not work for patients. While CML has become a manageable chronic condition for most patients on TKI therapy, long-term TKI use presents challenges that impact HRQOL, including symptoms, financial burden, and long-term toxicities. An active management approach will use supportive care to manage symptoms and prevent toxicities, dose reductions, switching TKIs when necessary, and pursuing TFR for eligible patients.

Tailoring treatment strategies to individual patient needs and preferences—particularly through authentic shared decision-making that incorporates regular symptom monitoring in addition to disease monitoring—is critical to optimizing outcomes. Continued research and patient-centered care models will be key to further improving the HRQOL for individuals living with CML.

References

1. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med*. 2001;344(14):1031-1037.
2. Druker BJ, Guilhot F, O'Brien SG, et al. Five-Year Follow-up of Patients Receiving Imatinib for Chronic Myeloid Leukemia. *N Engl J Med*. 2006;355(23):2408-2417.
3. Cortes JE, Saglio G, Kantarjian HM, et al. Final 5-Year Study Results of DASISION: The Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients Trial. *J Clin Oncol*. 2016;34(20):2333-2340.
4. Kantarjian HM, Hughes TP, Larson RA, et al. Long-term outcomes with frontline nilotinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: ENESTnd 10-year analysis. *Leukemia*. 2021;35(2):440-453.
5. Brümmendorf TH, Cortes JE, Milojkovic D, et al. Bosutinib (BOS) Versus Imatinib for Newly Diagnosed Chronic Phase (CP) Chronic Myeloid Leukemia (CML): Final 5-Year Results from the Bfore Trial. *Blood*. 2020;136(Supplement 1):41-42.
6. Cortes JE, Apperley J, Hochhaus A, et al. Outcome By Mutation Status and Line of Treatment in Optic, a Dose-Ranging Study of 3 Starting Doses of Ponatinib in Patients with CP-CML. *Blood*. 2020;136(Supplement 1):44-45.
7. Réa D, Mauro MJ, Boquimpani C, et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. *Blood*. 2021;138(21):2031-2041.
8. Cortes JE, Hughes TP, Mauro MJ, et al. Asciminib, a First-in-Class STAMP Inhibitor, Provides Durable Molecular Response in Patients (pts) with Chronic Myeloid Leukemia (CML) Harboring the T315I Mutation: Primary Efficacy and Safety Results from a Phase 1 Trial. *Blood*. 2020;136(Supplement 1):47-50.
9. Efficace F, Cardoni A, Cottone F, Vignetti M, Mandelli F. Tyrosine-kinase inhibitors and patient-reported outcomes in chronic myeloid leukemia: a systematic review. *Leuk Res*. 2013;37(2):206-213.
10. Phillips KM, Pinilla-Ibarz J, Sotomayor E, et al. Quality of life outcomes in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors: a controlled comparison. *Support Care Cancer*. 2013;21(4):1097-1103.
11. Steegmann JL, Cervantes F, le Coutre P, Porkka K, Saglio G. Off-target effects of BCR-ABL1 inhibitors and their potential long-term implications in patients with chronic myeloid leukemia. *Leuk Lymphoma*. 2012;53(12):2351-2361.
12. Cirmi S, El Abd A, Letinier L, Navarra M, Salvo F. Cardiovascular Toxicity of Tyrosine Kinase Inhibitors Used in Chronic Myeloid Leukemia: An Analysis of the FDA Adverse Event Reporting System Database (FAERS). *Cancers (Basel)*. 2020;12(4):826.
13. Jain P, Kantarjian H, Boddur PC, et al. Analysis of cardiovascular and arteriothrombotic adverse events in chronic-phase CML patients after frontline TKIs. *Blood Adv*. 2019;3(6):851-861.
14. Ren X, Qin Y, Huang X, Zuo L, Jiang Q. Assessment of chronic renal injury in patients with chronic myeloid leukemia in the chronic phase receiving tyrosine kinase inhibitors. *Ann Hematol*. 2019;98(7):1627-1640.
15. Marcolino MS, Boersma E, Clementino NCD, et al. Imatinib treatment duration is related to decreased estimated glomerular filtration rate in chronic myeloid leukemia patients. *Ann Oncol*. 2011;22(9):2073-2079.
16. Yilmaz M, Lahoti A, O'Brien S, et al. Estimated glomerular filtration rate changes in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. *Cancer*. 2015;121(21):3894-3904.
17. Lodish MB, Stratakis CA. Endocrine side effects of broad-acting kinase inhibitors. *Endocr Relat Cancer*. 2010;17(3):R233-244.

18. Zukas AM, Schiff D. Neurological complications of new chemotherapy agents. *Neuro Oncol.* 2017;20(1):24-36.
19. Orlandi EM, Rocca B, Pazzano AS, Ghio S. Reversible pulmonary arterial hypertension likely related to long-term, low-dose dasatinib treatment for chronic myeloid leukaemia. *Leuk Res.* 2012;36(1):e4-6.
20. Parthvi R, Gibbons W. Pulmonary Arterial Hypertension Worsened by Bosutinib in Patient With Previous Dasatinib Treatment. *Am J Ther.* 2020;28(6):e704-e706.
21. Weatherald J, Bondeelle L, Chaumais MC, et al. Pulmonary complications of Bcr-Abl tyrosine kinase inhibitors. *Eur Respir J.* 2020;56(4):21000279.
22. Kronick O, Chen X, Mehra N, et al. Hematological Adverse Events with Tyrosine Kinase Inhibitors for Chronic Myeloid Leukemia: A Systematic Review with Meta-Analysis. *Cancers (Basel).* 2023;15(17):4354.
23. Experts in Chronic Myeloid Leukemia. The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts. *Blood.* 2013;121(22):4439-4442.
24. Kantarjian H, Paul S, Thakkar J, Jabbour E. The influence of drug prices, new availability of inexpensive generic imatinib, new approvals, and post-marketing research on the treatment of chronic myeloid leukaemia in the USA. *Lancet Haematol.* 2022;9(11):e854-e861.
25. Winn AN, Keating NL, Dusetzina SB. Factors Associated With Tyrosine Kinase Inhibitor Initiation and Adherence Among Medicare Beneficiaries With Chronic Myeloid Leukemia. *J Clin Oncol.* 2016;34(36):4323-4328.
26. Shah NP, Bhatia R, Altman JK, et al. Chronic Myeloid Leukemia, Version 2.2024, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2024;22(1):43-69.
27. Apperley JF, Milojkovic D, Cross NCP, et al. 2025 European LeukemiaNet recommendations for the management of chronic myeloid leukemia. *Leukemia.* 2025;39(8):1797-1813.
28. Flynn KE, Mauro MJ, George G, et al. Patients' perspectives on the definition of cure in chronic myeloid leukemia. *Leuk Res.* 2019;80:40-42.
29. Flynn KE, Myers JM, D'Souza A, Schiffer CA, Thompson JE, Atallah E. Exploring Patient Decision Making Regarding Discontinuation of Tyrosine Kinase Inhibitors for Chronic Myeloid Leukemia. *Oncologist.* 2019;24(9):1253-1258.
30. Atallah EL, Broder MS, Chan O, et al. U.S. Expert Consensus on Defining Intolerance to Tyrosine Kinase Inhibitor Treatment in Chronic Phase Chronic Myeloid Leukemia (CML). *Blood.* 2024;144(Supplement 1):5052.
31. Nasa P, Jain R, Juneja D. Delphi methodology in healthcare research: How to decide its appropriateness. *World J Methodol.* 2021;11(4):116-129.
32. Jim HSL, Hyland KA, Nelson AM, et al. Internet-assisted cognitive behavioral intervention for targeted therapy-related fatigue in chronic myeloid leukemia: Results from a pilot randomized trial. *Cancer.* 2020;126(1):174-180.
33. Cornelison M, Jabbour EJ, Welch MA. Managing side effects of tyrosine kinase inhibitor therapy to optimize adherence in patients with chronic myeloid leukemia: the role of the midlevel practitioner. *J Support Oncol.* 2012;10(1):14-24.
34. Douxfils J, Haguet H, Mullier F, Chatelain C, Graux C, Dogne JM. Association Between BCR-ABL Tyrosine Kinase Inhibitors for Chronic Myeloid Leukemia and Cardiovascular Events, Major Molecular Response, and Overall Survival: A Systematic Review and Meta-analysis. *JAMA Oncol.* 2016;2(5):625-632.
35. Senapati J, Sasaki K, Issa GC, et al. Management of chronic myeloid leukemia in 2023 - common ground and common sense. *Blood Cancer J.* 2023;13(1):58.
36. Iurlo A, Cattaneo D, Bucelli C, Breccia M. Dose Optimization of Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia: A New Therapeutic Challenge. *J Clin Med.* 2021;10(3):515.
37. Deininger M, O'Brien SG, Guilhot F, et al. International Randomized Study of Interferon Vs STI571 (IRIS) 8-Year Follow up: Sustained Survival and Low Risk for Progression or Events

in Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Treated with Imatinib. *Blood*. 2009;114(22):1126.

38. Jabbour E, Sasaki K, Haddad FG, et al. Low-dose dasatinib 50 mg/day versus standard-dose dasatinib 100 mg/day as frontline therapy in chronic myeloid leukemia in chronic phase: A propensity score analysis. *Am J Hematol*. 2022;97(11):1413-1418.
39. Kantarjian H, Giles F, Wunderle L, et al. Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. *N Engl J Med*. 2006;354(24):2542-2551.
40. Rea D, Cayuela J-M, Dulucq S, Etienne G. Molecular Responses after Switching from a Standard-Dose Twice-Daily Nilotinib Regimen to a Reduced-Dose Once-Daily Schedule in Patients with Chronic Myeloid Leukemia: A Real Life Observational Study (NILO-RED). *Blood*. 2017;130(Supplement 1):318.
41. Larson RA, Druker BJ, Guilhot F, et al. Imatinib pharmacokinetics and its correlation with response and safety in chronic-phase chronic myeloid leukemia: a subanalysis of the IRIS study. *Blood*. 2008;111(8):4022-4028.
42. Picard S, Titier K, Etienne G, et al. Trough imatinib plasma levels are associated with both cytogenetic and molecular responses to standard-dose imatinib in chronic myeloid leukemia. *Blood*. 2007;109(8):3496-3499.
43. Forrest DL, Trainor S, Brinkman RR, et al. Cytogenetic and molecular responses to standard-dose imatinib in chronic myeloid leukemia are correlated with Sokal risk scores and duration of therapy but not trough imatinib plasma levels. *Leuk Res*. 2009;33(2):271-275.
44. Racil Z, Razga F, Klamova H, et al. No clinical evidence for performing trough plasma and intracellular imatinib concentrations monitoring in patients with chronic myelogenous leukaemia. *Hematol Oncol*. 2014;32(2):87-93.
45. Yoshida C, Komeno T, Hori M, et al. Adherence to the standard dose of imatinib, rather than dose adjustment based on its plasma concentration, is critical to achieve a deep molecular response in patients with chronic myeloid leukemia. *Int J Hematol*. 2011;93(5):618-623.
46. Rousselot P, Mollica L, Guilhot J, et al. Dasatinib dose optimisation based on therapeutic drug monitoring reduces pleural effusion rates in chronic myeloid leukaemia patients. *Br J Haematol*. 2021;194(2):393-402.
47. Yeung D, Grigg A, Shanmuganathan N, et al. P720: PROACTIVE DASATINIB DOSE REDUCTION IN THE ALLG CML 12 DIRECT STUDY BASED ON TROUGH LEVELS MINIMISE TOXICITY AND PRESERVE EFFICACY. *HemaSphere*. 2022;6:615-616.
48. Clark RE, Polydoros F, Apperley JF, et al. De-escalation of tyrosine kinase inhibitor therapy before complete treatment discontinuation in patients with chronic myeloid leukaemia (DESTINY): a non-randomised, phase 2 trial. *Lancet Haematol*. 2019;6(7):e375-e383.
49. Cayssials E, Torregrosa-Diaz J, Gallego-Hernanz P, et al. Low-dose tyrosine kinase inhibitors before treatment discontinuation do not impair treatment-free remission in chronic myeloid leukemia patients: Results of a retrospective study. *Cancer*. 2020;126(15):3438-3447.
50. Cortes JE, Apperley J, Lomaia E, et al. OPTIC primary analysis: A dose-optimization study of 3 starting doses of ponatinib (PON). *J Clin Oncol*. 2021;39(15_suppl):7000.
51. V.V.A.A. Ariad suspends ponatinib sales. *Cancer Discov*. 2014;4(1):6-7.
52. Lipton JH, Chuah C, Guerci-Bresler A, et al. Ponatinib versus imatinib for newly diagnosed chronic myeloid leukaemia: an international, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2016;17(5):612-621.
53. Ureshino H, Takahashi N, Ikezoe T, et al. Lower-Initiating Dose of Bosutinib for Resistant or Intolerant to Prior Therapy Chronic Myeloid Leukemia Patients (BOGI trial): A Single-Arm, Multicenter, Phase II Trial. *Blood*. 2023;142(Supplement 1):3179.

54. Kota V, Brümmendorf TH, Gambacorti-Passerini C, et al. Efficacy and safety following bosutinib dose reduction in patients with Philadelphia chromosome-positive leukemias. *Leuk Res.* 2021;111:106690.
55. Lokhorst DN, Smit Y, Van den Bemt BJB, et al. Interim analysis of a multicenter study on patient-guided dose reduction of tyrosine kinase inhibitors in chronic myeloid leukemia: the RODEO study. *Haematologica.* 2025 Oct 2. doi:10.3324/haematol.2025.288516 [Epub ahead of print]
56. Lokhorst DN, Smit Y, Hermens PMG, van den Bemt BJB, Blijlevens NMA, Bekker CL. Prospective multicentre study (RODEO) investigating dose reduction of tyrosine kinase inhibitors (TKIs) in chronic myeloid leukaemia (CML). <https://simul-europe.com/2024/mascc/Files/2042.pdf> Accessed 9/6/2025.
57. Russo D, Malagola M, Skert C, et al. Managing chronic myeloid leukaemia in the elderly with intermittent imatinib treatment. *Blood Cancer J.* 2015;5(9):e347.
58. Hochhaus A, Wang J, Kim DW, et al. Asciminib in Newly Diagnosed Chronic Myeloid Leukemia. *N Engl J Med.* 2024;391(10):885-898.
59. Hochhaus A, Saglio G, Hughes TP, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. Original Article. *Leukemia.* 2016;30(5):1044-1054.
60. Brümmendorf TH, Cortes JE, Milojkovic D, et al. Bosutinib versus imatinib for newly diagnosed chronic phase chronic myeloid leukemia: final results from the BFORE trial. *Leukemia.* 2022;36(7):1825-1833.
61. Cortes JE, Lipton JH, Kota V, et al. Cross-intolerance with bosutinib after prior tyrosine kinase inhibitors for Philadelphia chromosome-positive leukemia: long-term analysis of a phase I/II study. *Haematologica.* 2023;108(12):3454-3459.
62. Jain AG, Gesiotto Q, Ball S, et al. Incidence of pleural effusion with dasatinib and the effect of switching therapy to a different TKI in patients with chronic phase CML. *Ann Hematol.* 2024;103(6):1941-1945.
63. Kobayashi Y, Sakamaki H, Fujisawa S, et al. Lack of non-hematological cross intolerance of dasatinib to imatinib in imatinib-intolerant patients with Philadelphia chromosome positive chronic myeloid leukemia or acute lymphatic leukemia: a retrospective safety analysis. *Int J Hematol.* 2011;93(6):745-749.
64. Khoury H, Goldberg S, Mauro M, et al. Dasatinib lack of cross intolerance to imatinib in patients (pts) with chronic myelogenous leukemia chronic phase (CML-CP) intolerant to imatinib: a retrospective analysis of safety. *J Clin Oncol.* 2008;26(15_suppl):7015.
65. Cortes JE, Hochhaus A, le Coutre PD, et al. Minimal cross-intolerance with nilotinib in patients with chronic myeloid leukemia in chronic or accelerated phase who are intolerant to imatinib. *Blood.* 2011;117(21):5600-5606.
66. Atallah EL, Mauro MJ, Sasaki K, et al. Dose-escalation of second-line and first-line asciminib in chronic myeloid leukemia in chronic phase: the ASC2ESCALATE Phase II trial. *Future Oncol.* 2024;20(38):3065-3075.
67. Atallah E, Andorsky DJ, Luskin M, et al. Interim analysis (IA) results from ASC2ESCALATE support asciminib (ASC) as a treatment (tx) option in chronic-phase chronic myeloid leukemia (CML-CP) after 1 tyrosine kinase inhibitor (TKI). *HemaSphere.* 2025;9(S1):563.
68. Werk RS, Mehrhoff CJ, Badawy SM. Quality of Life and Adherence to Tyrosine Kinase Inhibitors Among Pediatric, Adolescent, and Young Adult Chronic Myeloid Leukemia Patients: A Systematic Review. *Pediatr Blood Cancer.* 2025;72(6):e31686.
69. Tan BK, Bee PC, Chua SS, Chen LC. Monitoring and Improving Adherence to Tyrosine Kinase Inhibitors in Patients with Chronic Myeloid Leukemia: A Systematic Review. *Patient Prefer Adherence.* 2021;15:2563-2575.

70. Heiney SP, Sorrell M, Sheng J, et al. Interventions to Improve Adherence to Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia: A Systematic Review. *Am J Clin Oncol*. 2021;44(6):291-298.
71. Atallah E, Sweet K. Treatment-Free Remission: the New Goal in CML Therapy. *Curr Hematol Malig Rep*. 2021;16(5):433-439.
72. Atallah E, Schiffer CA, Radich JP, et al. Assessment of Outcomes After Stopping Tyrosine Kinase Inhibitors Among Patients With Chronic Myeloid Leukemia: A Nonrandomized Clinical Trial. *JAMA Oncol*. 2021;7(1):42-50.
73. Schoenbeck KL, Atallah E, Lin L, et al. Patient-Reported Functional Outcomes in Patients With Chronic Myeloid Leukemia After Stopping Tyrosine Kinase Inhibitors. *J Natl Cancer Inst*. 2022;114(1):160-164.
74. Flynn KE, Atallah E, Lin L, et al. Patient- and physician-reported pain after tyrosine kinase inhibitor discontinuation among patients with chronic myeloid leukemia. *Haematologica*. 2022;107(11):2641-2649.
75. Winn AN, Atallah E, Cortes J, et al. Estimated Savings After Stopping Tyrosine Kinase Inhibitor Treatment Among Patients With Chronic Myeloid Leukemia. *JAMA Netw Open*. 2023;6(12):e2347950.
76. Saussele S, Richter J, Guilhot J, et al. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial. *Lancet Oncol*. 2018;19(6):747-757.
77. Cortes JE, Jimenez CA, Mauro MJ, Geyer A, Pinilla-Ibarz J, Smith BD. Pleural Effusion in Dasatinib-Treated Patients With Chronic Myeloid Leukemia in Chronic Phase: Identification and Management. *Clin Lymphoma Myeloma Leuk*. 2017;17(2):78-82.
78. Nodzon L, Fadol A, Tinsley S. Cardiovascular Adverse Events and Mitigation Strategies for Chronic Myeloid Leukemia Patients Receiving Tyrosine Kinase Inhibitor Therapy. *J Adv Pract Oncol*. 2022;13(2):127-142.
79. Minson AG, Cummins K, Fox L, et al. The natural history of vascular and other complications in patients treated with nilotinib for chronic myeloid leukemia. *Blood Adv*. 2019;3(7):1084-1091.
80. Sweet K, Othus M, Tantravahi S, et al. A Phase 2, Randomized Trial Of Ruxolitinib in Addition to BCR::ABL1 TKIs in CML Patients With Molecular Evidence Of Disease (SWOG Trial S1712) *HemaSphere*. 2024;8(S174):e104.
81. Zeidan AM, Roopcharan K, Radich JP, et al. Minimal Toxicity Seen When Pembrolizumab Is Added to Tyrosine Kinase Inhibitors in Patients with Chronic Myeloid Leukemia and Persistently Detectable Minimal Residual Disease: Early Results from an Ongoing Phase II Trial (ECOG-ACRIN EA9171). *Blood*. 2021;138(Supplement 1):3613.
82. Mauro M, Visotcky A, Flynn KE, et al. Treatment Free Remission after Combination Therapy with Asciminib (ABL001) Plus Imatinib in Chronic Phase Chronic Myeloid Leukemia (CP-CML) Patients Who Relapsed after a Prior Attempt at TKI Discontinuation-H Jean Khoury Cure CML Consortium Study. *Blood*. 2022;140(Supplement 1):6765.
83. Sweet K, Atallah EL, Radich JP, et al. Second Treatment Free Remission after Combination Therapy with Ruxolitinib Plus Tyrosine Kinase Inhibitors in Chronic Phase Chronic Myeloid Leukemia (CML). *Blood*. 2021;138(Supplement 1):2555.
84. Yamada M, Kuroda H, Shimoyama S, et al. [Efficacy of levocarnitine for tyrosine kinase inhibitor-induced painful muscle cramps in patients with chronic myelogenous leukemia]. *Rinsho Ketsueki*. 2016;57(4):489-491.
85. Jang A, Brown C, Lamoury G, et al. The Effects of Acupuncture on Cancer-Related Fatigue: Updated Systematic Review and Meta-Analysis. *Integr Cancer Ther*. 2020;19:1534735420949679.
86. Clark RE, Polydoros F, Apperley JF, et al. De-escalation of tyrosine kinase inhibitor dose in patients with chronic myeloid leukaemia with stable major molecular response (DESTINY):

an interim analysis of a non-randomised, phase 2 trial. *Lancet Haematol.* 2017;4(7):e310-e316.

87. Cervantes F, Correa JG, Pérez I, et al. Imatinib dose reduction in patients with chronic myeloid leukemia in sustained deep molecular response. *Ann Hematol.* 2017;96(1):81-85.
88. Shukhov O, Gurianova M, Chelysheva E, et al. Results of the Molecular Response Evaluation and TKI Dose Adjustment in Chronic Myeloid Leukemia Patients in Prospective Study of Reduction and Discontinuation Treatment of TKI (READIT). *Blood.* 2024;144(Supplement 1):4539.

Table 1: Guideline- or expert-based supportive care management of common symptoms related to TKI use

Symptom	Supportive Care Options
Diarrhea	Antidiarrheal medications (e.g., loperamide) Dietary adjustments
Muscle cramps	Magnesium or calcium replacement Levocarnitine ⁸⁴ Stretching Hydration Analgesics (e.g., acetaminophen, non-steroidal anti-inflammatory drugs)
Fatigue	Exercise Cognitive behavioral therapy ³² Yoga Acupuncture ⁸⁵ Manage contributing factors (anemia, thyroid issues, sleep disturbances)
Fluid retention	Salt restriction Leg elevation, compression stockings Diuretics
Nausea	Take TKI with food (imatinib, dasatinib and bosutinib) Small frequent meals Antiemetics (e.g., ondansetron)
Skin rash/itching	Topical corticosteroids Antihistamines Skin moisturizers Gentle skin care Systemic corticosteroids
Headaches/Musculoskeletal pain	Analgesics (acetaminophen, non-steroidal anti-inflammatory drugs) Heat/cold therapy Stretching
Mood/sleep disturbances	Sleep hygiene Exercise Counseling/psychological support Medication review
Dyspnea	Evaluate etiology and manage underlying condition Thoracentesis

Table 2. Published studies of TKI dose reduction

Study	TKI	Design	BCR::ABL1 threshold for dose reduction	BCR::ABL1 threshold for dose increase	CML Response	Clinician-reported AEs	PROs
CML12 (DIRECT) ⁴⁷	dasatinib	Dasatinib 100 mg. Dose reduced to 70 mg then 50 mg based on cmin at 7, 28, 56 and 90 days (n=80)	NA	NA	83% of patients reduced dose by 28 days. At month 24 10%, 18%, and 51% were on 100, 70 and 50 mg, respectively	Improved tolerability, particularly with respect to plural effusions	Not collected
NILO-RED ⁴⁰ (France)	nilotinib	Reduce from 2x daily dose to 1x daily dose for convenience (n=67)	<0.1%	>0.1%	2 patients lost MR 3 but regained it after 4 months without increasing the dose	Improved tolerability, minimal AE recurrence	Not collected
DESTINY ^{48,86} (United Kingdom)	dasatinib imatinib nilotinib	Reduce dose to 50% for 1 year then discontinue to try for TFR (n=173)	<0.1%	>0.1%	20% lost MR 3 & returned to full dose; 80% tried TFR, of whom 50% lost MR 3 and returned to full dose	Common chronic AEs (lethargy, diarrhea, rash, nausea, periorbital edema, and hair thinning) improved on lower dose	FACT-BRM & EQ-5D were collected but not reported ⁸⁶
OPTIC ⁶ (international)	ponatinib	Start advanced patients on 45, 30, or 15 mg, then reduce dose (n=283)	≤1%	>1%	MR 2 was reached by 42%, 28%, and 24% of patients in the 45, 30, and 15 mg starting groups, respectively	Lower incidence of arterial occlusive events and other toxicities	Not collected
CML Spanish Group (GELMC) study ⁸⁷	imatinib	Reduce dose from 400 to 300 mg for patients with sustained deep response. (n=43)	<0.01%		1 patient lost MR 4, no patients lost MR 3	Improved tolerability, 54% of patients with side effects had complete resolution	Not collected
OPTIM-	dasatinib	Patients on 100	NA	NA	No significant	Pleural and	Not collected

dasatinib ⁴⁶ (France)		mg with a dasatinib level > 3 nmol/l by TDM were randomized to continue same dose or reduce to lower dose (n=80)			difference in MR 3 rates between the TDM reduced dose arm (78%) and control arm (59%)	pericardial effusions were reduced in the TDM reduced dose arm (13%) compared to the control arm (43%)	
RODEO ^{55,56} (Netherlands)	imatinib, dasatinib, nilotinib, bosutinib, ponatinib	Dose reduction based on shared decision making between patient and physician (n=147, results are for n=97 included in 12-month interim results)	<0.1%; of note, 92% of participants at <0.01% at baseline	>0.1% or expected loss of MR3, e.g. due to ≥ 1 log increase compared to baseline molecular status	3 patients lost MR 3, 3 other patients increased dose without loss of MR 3, 1 because of expected loss of MR 3, and 2 because they chose to; the median relative dose reduction at 6 months was 25% of the initial dose	Not reported	EORTC QLQ-C30 and QLQ-CML24: medium-sized improvement in social functioning and small improvements in fatigue, GI symptoms, impact on daily life, and body image
READIT ⁸⁸ (Russian Federation)	imatinib, dasatinib, nilotinib, bosutinib	2 phases: I) doses were approx. halved, if DMR maintained, then II) dose was halved again, followed by attempted TKI discontinuation if eligible (n=103)	<0.01%; of note, 95% of participants at $\leq 0.0032\%$ at baseline	>0.1%	In phase I, 1 patient lost MR 3, 4 patients lost MR 4 In phase II, 4 patients lost MR 3 and 13 patients lost MR 4 All patients regained MR 3 with TKI increases	Not reported	Not collected

AE: Adverse events, PROs: Patient reported outcomes, MR: molecular response

Table 3. Select cross-intolerance symptoms and signs

First TKI Drug	Intolerance to first TKI	Second TKI	Recurrence of AE	Discontinuation for same AE
imatinib ⁶¹	Diarrhea	bosutinib	84.6%	7.7%
imatinib ⁶¹	Thrombocytopenia	bosutinib	79.4%	32.4%
dasatinib ⁶¹	Thrombocytopenia	bosutinib	100%	38.5%
dasatinib ^{61,62}	Plural effusions	bosutinib	46-52%	8.7%
imatinib ⁶³	Hematological toxicity	dasatinib	NR	13%
imatinib ⁶⁵	Hematological toxicity	nilotinib	57.5%	18%